REMARKS

Claims 1, 3, 5, 7, 8, 10, 11, and 13-16 are pending in the application. Claims 2, 4, 6, 9 and 12 have been cancelled. Claims 1, 7, 10 and 13 have been amended. Claims 14-16 are newly added. Support for the amendments is found in the specification at page 11. No new matter has been added.

Claims 7-12 and 13 have been rejected under 35 U.S.C.§112, first paragraph as allegedly not enabled by the specification. Applicants respectfully traverse this rejection.

The Examiner questions whether the specification is enabling for the treatment of neurological and neurobehavioural disorders other than ischemia. Applicants submit that one of ordinary skill in the art would deem the claims enabling for other neurological and neurobehavioural disorders in which Glu toxicity occurs.

The Applicants provide the following explanation of how pGLU-GLU-PRO-amide (EEP) is neuroprotective in injuries and diseases wherein excessive amounts of Glu are released.

Glu-induced neurotoxicity caused by injury or disease

Excessive amounts of Glu are toxic to neurons in culture and in the body. The excitatory amino acid neurotransmitter, Glu, opens membrane channels providing for a massive influx of both Na+ and Ca2+ ions. The resulting depolarization, in turn, opens voltage-gated cation channels, and exhausts neuronal energy reserves, as an effort is made to restore homeostasis. Neuronal viability decreases with increasing concentration of Glu.

EEP provides neutoprotection against Glu-induced neurotoxicity

EEP has been found by the present inventors to be neuroprotective in vitro against an excitotoxic insult of Glu. To evaluate the possibility that EEP would reduce the damage associated with prolonged excitatory activity, the inventors conducted a series of in vitro experiments using prolonged exposure to Glu to excite neuron-rich cultures. The

inventors verified that EEP is neuroprotective in cultures derived from both forebrain and spinal cord. (See present specification and Koenig 2001.)

EEP crosses the brain barrier when injected by IV or IP.

On the bottom of page 2 of the Office Action, the Examiner states that unlike TRH, the pGLU-GLU-PRO-amide does not enter the brain. This is not correct. The Applicants have stated and shown that EEP does enter the brain. "EEP, after IP or IV administration, is readily taken up by and has a long residence time in the brain tissue." Pekary, 1999, p. 107, Abstract, final sentence.

It is known that EEP is present in the hippocampus, a part of the brain which is essential for important aspects of memory. The inventors have shown that EEP is as much as four times more effective as a neuroprotectant than TRH (Koenig et al., 2001) in neurons derived from brain or spinal cord .

EEP is not attacked by enzyme thyroliberinase.

Further, EEP is not attacked by thyroliberinase. "Interestingly, EEP, an endogenous TRH-like peptide, is not metabolized by thyroliberinase, a blood enzyme which specifically inactivated TRH." Pekary, 2000, p. 175, col. 1, second paragraph. It is now known that peripherally administered TRH is attacked and degraded in the bloodstream by the enzyme thyroliberinase and has a serum half life of only 5.3 minutes (Marangell et al., 1997). This severely limits the capacity of parenterally administered TRH to penetrate the CNS. In marked contrast to TRH, pGlu-Glu-Pro-amide (EEP) is not attacked by thyroliberinase (Pekary et al., 2000; O'Cuinn, 1995) and administered peripherally, does in fact enter the brain, where levels remain elevated for hours (Pekary et al., 1999). EEP is also less readily hydrolyzed than TRH in vivo.

EEP is safe to administer to a patient.

EEP is an endogenous compound to the brain and spinal cord.

Conclusion

The fact that EEP enters the brain and spinal cord, has been shown to give neuroprotection against Glu induced neurotoxicity, and is not degraded by thyroliberinase would be recognized by one skilled in therapeutic arts that it is therapeutically beneficial in attenuating the progression of and ameliorating symptoms of neurodegenerative diseases wherein excessive amounts of toxic Glu are present.

Claims 1-2 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Cremades, et al. Applicants respectfully traverse this rejection.

Claim 1, as amended, is directed to a composition having a neuroprotective amount of pGLU-GLU-PRO-amide in a pharmaceutically acceptable carrier, wherein said neuroprotective amount is an amount sufficient to reduce Glu induced neurotoxicity in brain, spinal cord and/or retina.

Cremades et al. is directed to the use of pGlu-Glu-Pro-amide to affect the pituitary gland. In order to anticipate claim 1, a neuroprotective amount sufficient to reduce Glu induced neurotoxicity in brain, spinal cord and/or retina must be disclosed by Cremades et al. Cremades et al. does not teach a neuroprotective amount as defined by amended claim 1. Cremades et al. teaches nothing about what amount would constitute an neuroprotective amount or even the ability of pGlu-Glu-Pro-amide (EEP) to be neuroprotective or cross the blood-brain barrier. Cremades only teaches that EEP was given and may have reached and acted on the pituitary gland, which is outside the blood-brain barrier (i.e. no disclosure of neuroprotectivity or what amount is needed to be neuroprotective).

Cremades teaches nothing about formulations necessary for administering a compound to the central nervous system, or any part thereof. Moreover, Cremades et al. states about EEP, "[O]ur understanding of their physiological roles, however, is not yet complete." (page 63, clolum 2, lines 3-4.) Hence, Cremades does not anticipate the present invention under 35 U.S.C. 102(b).

Reconsideration is respectfully requested.

Respectfully submitted,

Date: Feb 24, 2003 By

Caroline Nash, Reg. No. 36, 329
for: Elizabeth Arwine, Reg. No. 45,867
U.S. Army Medical Research
and Materiel Command
ATTN: MCMR-JA
Fort Detrick, MD 21702-5012

Nash & Titus, LLC
3415 Brookeville Road, Suite 1000
Brookeville, MD 20833
(301) 924-9500

Versions with markings to show changes made.

IN THE CLAIMS:

Please cancel claims 9 and 12.

Please amend the claims as follows:

1. (Twice Amended) A pharmaceutical composition comprising a [neuroprotectant] neuroprotective amount of pGLU-GLU-PRO-amide as an active ingredient and a pharmaceutically acceptable carrier, wherein said neuroprotective amount is an amount sufficient to reduce Glu induced neurotoxicity in brain, spinal cord and/or retina.

7. (Twice Amended) A method of [treating neurological diseases and injuries] reducing Glu induced neurotoxicity in brain, spinal cord and/or retina comprising administering to a patent a composition comprising a therapeutically effective amount of pGLU-GLU-PRO-NH_2 as an active ingredient under time and conditions to treat said Glu induced neurotoxicity [disease].

10. (Twice Amended) A method of [treating neurological diseases and injuries] reducing Glu induced neurotoxicity in brain, spinal cord and/or retina comprising administering to a patient a composition comprising a therapeutically effective amount of (a) pGLU-GLU-PRO-NH_2 and (b) N-tert-Butyl-α-(2-sulfophenyl) nitrone or a free radical scavenging nitrone that enhances the effects of pGLU-GLU-PRO-NH_2 under time and conditions to treat said Glu induced neurotoxicity [disease].

13. (Amended) A method of preventing [neurological diseases and injuries] Glu induced neurotoxicity in brain, spinal cord and/or retina comprising administering to a patent a composition comprising a therapeutically effective amount of pGLU-GLU-PRO-NH_2 as an active ingredient under time and conditions to treat said Glu induced neurotoxicity [disease].

Please add the following claims:

---14. (New) The composition of claim 1, wherein said neuroprotective amount is about 0.5 to 10 mg per kilogram of body weight per dose.

15. (New) The composition of claim 1, wherein said pharmaceutically acceptable carrier is one or more ingredients selected from the group consisting of: starch, sugar, flavoring agents, preservatives, water, organic co-solvents, flavor emulsions, oils and elixirs.

16. (New) The composition of claim 1, wherein said pharmaceutically acceptable carrier affords prolonged action or sustained release. ---.